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Diaphragmatic Hernia-Exomphalos-Hypertelorism Syndrome: A New Case and Further Evidence of Autosomal Recessive Inheritance

Karen W. Gripp,[1*] Dian Donnai,[3] Carol L. Clericuzio,[4] Donna M. McDonald-McGinn,[1] Marta Guttenberg,[2] and Elaine H. Zackai[1]

[1]*Division of Human Genetics and Molecular Biology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania*
[2]*Department of Pathology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania*
[3]*Regional Genetic Service, St. Mary's Hospital, Manchester, United Kingdom*
[4]*University of New Mexico School of Medicine, Albuquerque*

We describe a male patient with wide anterior fontanel and metopic suture, hypertelorism, down slanting palpebral fissures, bilateral iris coloboma, omphalocele, and bilateral absence of the diaphragm with herniation of abdominal organs causing pulmonary hypoplasia and death. Autopsy also showed intestinal malrotation. All findings in this case are consistent with those described as a newly recognized syndrome by Donnai and Barrow [1993]. Since the parents are first cousins, this case provides further evidence for the previously postulated autosomal recessive inheritance pattern. Follow-up on the patients and families reported by Donnai and Barrow [1993] also supports autosomal recessive inheritance. Am. J. Med. Genet. 68:441–444, 1997.

KEY WORDS: absent corpus callosum; autosomal recessive inheritance; diaphragmatic hernia; hypertelorism; exomphalos; iris coloboma; sensorineural deafness; myopia

INTRODUCTION

Recently we studied a patient with wide anterior fontanel and metopic suture, hypertelorism, downslanting palpebral fissures, bilateral iris coloboma diaphragmatic hernia, and exomphalos. These findings are those of a syndrome described by Donnai and Barrow [1993]. Other findings in this syndrome include absent corpus callosum, myopia, sensorineural deafness, iris coloboma, short nose with a broad tip, and intestinal malrotation. None of the parents manifested any of these findings and chromosomes were normal in all cases. Autosomal recessive inheritance was suspected because two sets of sibs, a boy and a girl in each, were affected and the parents of another patient were possibly distantly related.

CLINICAL REPORT

The male infant was the third child born to first cousin parents from Saudi Arabia. The 29-year-old mother and the 30-year-old father are healthy, as are the two older sisters. The mother previously had an ectopic pregnancy. In this pregnancy there was no reported problem and no prenatal exposure. Spontaneous vaginal breech delivery occurred at term and polyhydramnios was noted. The infant required immediate intubation, but could not be ventilated and died after 2 hours due to pulmonary hypoplasia.

Birthweight was 3.3 kg (50–75th centile), length was 48 cm (25–50th centile), and OFC 37.5 cm (>97th centile). Autopsy showed wide anterior fontanel (5 × 7 cm), wide metopic suture and frontal bossing (Fig. 1), nevus flammeus over the forehead, downslanting palpebral fissures, hypertelorism (inner canthal distance 3.8 cm; outer canthal distance 8 cm, both >97th centile), and bilateral iris coloboma. The nose appeared very broad from bridge to tip. Lips were slightly thin, the frenulum almost bisected the upper gum, and palate was intact. The ears appeared posteriorly angulated (Fig. 2). A small omphalocele was noted (Fig. 3). Dermatoglyphics were normal. Autopsy showed bilateral absence of the diaphragm with the left liver lobe in the left and the spleen in the right hemithorax. Intestinal malrotation was present. On the parents' request the autopsy did not include examination of the brain. Chromosomes (blood lymphocytes) were apparently normal (46,XY).

DISCUSSION

The findings in our patient are similar to those described in a newly recognized syndrome by Donnai and

*Correspondence to: Karen W. Gripp, Clinical Genetics, Children's Hospital of Philadelphia, 34th and Civic Center Boulevard, Philadelphia, PA 19104.

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Fig. 1. Postmortem photograph: note open metopic suture, frontal bossing, down-slant of palpebral fissures, hypertelorism, broad nose, and thin upper lip.

Fig. 2. Postmortem photograph; note posteriorly angulated ear, and flat facial profile.

Barrow [1993]. They report two liveborn, unrelated patients with large anterior fontanel, hypertelorism, short nose, diaphragmatic hernia, exomphalos, intestinal malrotation, and absent corpus callosum. These patients, a boy and a girl, also had sensorineural hearing loss and myopia, and one of them had a unilateral iris coloboma. Because in each of these families there was a similarly affected fetus of opposite sex to the index case, and possible consanguinity in a third family, an autosomal recessive inheritance pattern was suspected. Follow-up on the pedigrees shows further evidence for this inheritance pattern. Family 1 in the report by Donnai and Barrow [1993] had an additional affected fetus (Fig. 4; Family 1). In family 2 a healthy daughter was born after a pregnancy monitored for diaphragmatic and anterior abdominal wall defects (Fig. 4; Family 2). The parents described in a "note added in proof" in the paper by Donnai and Barrow [1993] are probably second cousins once removed; the propositus has a healthy half-sister (Fig. 4; Family 3). The parents of our patient are first cousins (Fig. 4; Family 4) providing additional evidence for the autosomal inheritance pattern.

Holmes and Schepens [1972] reported a brother and a sister with more severe eye abnormalities, telecanthus, sensorineural deafness, and umbilical hernia in the boy. Since neither child had a diaphragmatic hernia and the corpus callosum was not commented on in these patients, it is unclear if they had the syndrome described by Donnai and Barrow. Interestingly, the boy also had an iris coloboma and retinal detachment; however, his eye abnormalities were more extensive. He was intellectually handicapped, while his sister was of normal intelligence. This family's pedigree (Fig. 4; Family 5) is consistent with autosomal recessive inheritance.

Since the original article by Donnai and Barrow [1993] was published, more information about the patients has become available. Patient 1 is now 9 years old and attends a school for children with hearing disabilities. He communicates by signing and some words. He has little useful vision in his left eye with iris

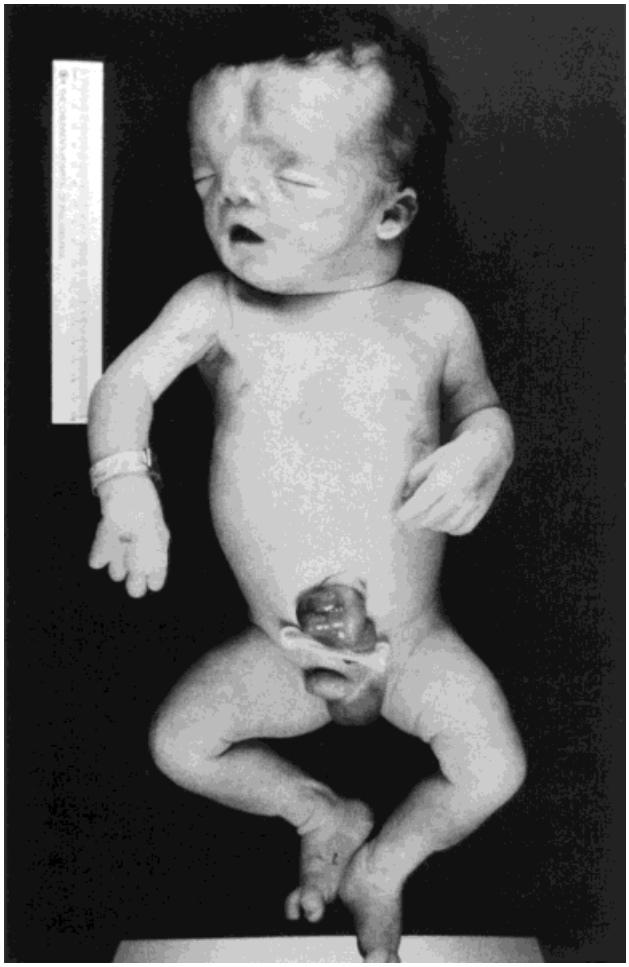

Fig. 3. Postmortem photograph: note omphalocele.

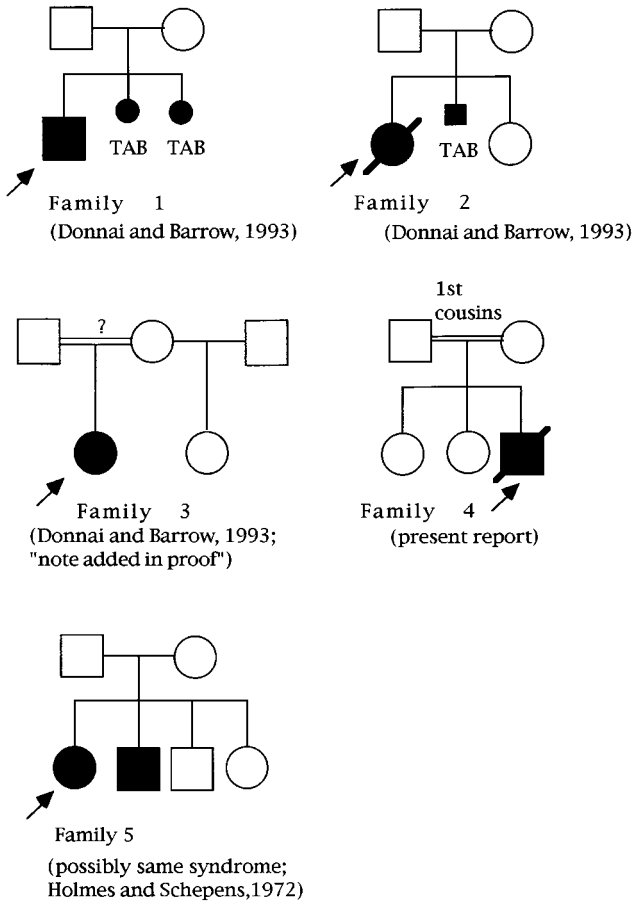

Fig. 4. Updated pedigrees reported by Donnai and Barrow [1993] (families 1–2; family 3 is "note added in proof"). Family 4 is described in this report. Family 5 corresponds to the one presented by Holmes and Schepens [1972], who possibly shared the same syndrome. TAB, therapeutic abortion.

coloboma and retinal detachment. His development is more delayed than expected for his disabilities. At 7 years a CT scan confirmed divergence of the lateral ventricles, consistent with agenesis of the corpus callosum. EEG was normal.

Ultrasound examination of an additional pregnancy in family 1 showed that the female fetus had exomphalos, left diaphragmatic hernia, and absent corpus callosum. The pregnancy was terminated at 17 weeks. Autopsy showed large anterior and posterior fontanels and there was obvious hypertelorism (inner canthal distance 1.7 cm, outer canthal distance 3.1 cm). Posteriorly angulated ears and micrognathia were present. The exomphalos measured 1.7 cm in diameter and contained 9 mm of large intestine, the appendix, and approximately half of the small intestine. A diaphragmatic hernia containing part of the left lobe of the liver, the spleen, and the fundus of the stomach displaced the left lung. There was a double outlet right ventricle, with the aortic valve orifice lying on the posterior wall of the right ventricle behind and to the right of the pulmonary artery. A VSD measuring 2 mm in diameter was present beneath the pulmonary valve, and an intramuscular VSD had the same size. Absence of the corpus callosum was confirmed.

Patient 3 of the original report died at age 6 5/12 years. She had been in good health until 2 days prior, when she began to have seizures and developed a prolonged status epilepticus. On admission to the hospital she was febrile, collapsed, and failed to respond to intravenous fluid resuscitation. Detailed investigations did not confirm a focus of infection and bacteriological studies were negative. She became anuric and died before hemodialysis could be instituted. The cause of death was thought to be a prolonged status epilepticus and renal failure; autopsy was declined.

The girl described in the "note added in proof" is now 2 7/12 years old. During the pregnancy a right sided diaphragmatic hernia and absent corpus callosum were noted. She was delivered at term, birth weight was 3.3 kg, and OFC was 38.5 cm. Down-slanting palpebral fissures and hypertelorism were obvious (inner canthal distance 3.4 cm; outer canthal distance 8.2 cm; both >97th centile). Echocardiogram showed a patent foramen ovale, a VSD, and a small patent ductus arteriosus; brain ultrasound findings were consistent with

absent corpus callosum. The patient required mechanical ventilation prior to the surgical repair of the diaphragmatic hernia; postoperative recovery was good. An auditory brain stem response test showed no response at a maximum level of stimulation. Hearing aids were supplied within the first 5 months of her life but are not worn consistently. She communicates with signing and appears more alert and responsive to sound when she does wear her aids. High myopia of 17 diopters is present bilaterally. Examination under anesthesia demonstrated myopic fundus changes with gross attenuation of the retinal pigment epithelium. There was a cobblestone-like degeneration in both eyes, especially temporally just behind the ora serrata, and a cystic retinal tuft in the supero-temporal periphery of the left eye. In view of the extreme congenital myopia and the previous observation of retinal detachment in other patients with this disorder, peripheral retinal laser treatment was undertaken prophylactically. Developmental delay is more severe than expected with her visual and hearing problems.

In conclusion, our patient with consanguinity adds further support to the postulated autosomal recessive inheritance pattern in this syndrome. Because of the recurrence risk it is important to offer monitoring of future pregnancies to families with this syndrome. The finding of colobomata in our patient and patient 1 [Donnai and Barrow, 1993] shows that iris colobomata are part of the syndrome. The heart defects in the fetus of family 1 and in the patient in family 3 make it important to study other patients for cardiac abnormalities.

NOTE ADDED IN PROOF

This girl was born at 34.5 weeks of gestation to a 23-year-old G1 mother and a non-consanguineous 24-year-old father. Pregnancy was complicated by polyhydramnios and amniocentesis documented a normal 46,XX karyotype. There was no known teratogenic exposure. Delivery was by C-section for breech position, and Apgar scores were 1, 2 and 6 at 1, 5 and 10 minutes, respectively. The patient required immediate intubation, and a left diaphragmatic hernia was diagnosed on radiographs. The infant was considered a candidate for extracorporeal membrane oxygenation (ECMO); however, since she was noted to have an unusual craniofacial appearance, the clinical genetics service was consulted urgently for a possible syndrome diagnosis. On physical examination the weight was 2.7 kg (80th centile), length 46.5 cm (60th centile) and OFC 34.5 cm (98th centile). There was cranium bifidum occultum, hypertelorism and down-slanting palpebral fissures (Fig. 5). Bedside cranial ultrasound study showed absent corpus callosum. The severity of hypoxemia excluded the patient as an ECMO candidate, and she died at age 12 hours. Autopsy confirmed absence of corpus callosum, a diaphragmatic hernia, and a bicornuate uterus. Karyotype from blood lymphocytes was 46,XX at the 450 band level. The patient's phenotype was recognized as that reported by Donnai and Barrow [1993], and the couple was counselled as to the probable autosomal recessive inheritance of the disorder. They chose to pursue a second pregnancy utilizing artificial insemination by unrelated donor and subsequently had a healthy child.

Fig. 5. Patient described in the note added in proof. Postmortem photograph of the face shows hypertelorism and down-slanting palpebral fissures.

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